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EXAMINER	
KERR, KATHLEEN M	

ART UNIT	PAPER NUMBER
1652	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/980,217	LEADLEY ET AL.	
	Examiner	Art Unit	
	Kathleen M. Kerr	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 March 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5 and 7-49* is/are pending in the application.

4a) Of the above claim(s) *13-29,35,36 and 39-45* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7-12,30-34,37,38 and 46-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *See Continuation Sheet*.

KL

Continuation of Attachment(s) 6). Other: ATCC and copy of page 103 of WO 98/01546.

DETAILED ACTION

Application Status

1. In response to the previous Office action, a non-final rejection (mailed on August 25, 2004), Applicants filed a response and amendment received on January 27, 2005. Said amendment cancelled Claim 6, amended Claims1-3, 7, 8, 11, 30, 32, 34, and 46, and added new Claims 47-49. Thus, Claims 1-5 and 7-49 are pending in the instant Office action.

Election/Unity of Invention

2. Applicant's election with traverse of Group 13, Claims 1-3, 6-12, 30-34, 37, 38, 46 and 47 as drawn to MonAIV, in the reply filed on June 7, 2004 is reiterated. The instant application is a filing under 35 U.S.C. § 371; thus, lack of unity practice is the basis for restriction and must be assessed at each stage of prosecution.

Despite the fact that Claim 1 is now drawn to a DNA sequence encoding a part of a defined MonAIV protein (SEQ ID NO:22) thus obviating previous art rejections, new art is set forth below that anticipates AT5 of MonAIV (14221-15243 of SEQ ID NO:2). Thus, Claim 1 still lacks unity of invention for lacking a special technical feature.

However, due to amendments, other claims are now grouped with the technical feature of Claim 1. Claims 1-5, 7-12, 30-34, 37, 38, and 46-49 are drawn to inventions sharing the technical feature of Claim 1. Claims 13-29, 35, 36, and 38-45 are withdrawn from consideration as non-elected inventions.

Priority

3. As previously noted, the instant application is granted the benefit of priority for the International Application No. PCT/GB00/02072 filed on May 30, 2000 and for the foreign application 9912563.5 filed on May 28, 1999.

Information Disclosure Statement

4. The information disclosure statement filed on March 10, 2005 has been reviewed, and its references have been considered as shown by the Examiner's initials next to each citation on the attached copy.

Compliance with the Sequence Rules

5. By virtue of Applicant's amendment to the specification, the instant application now fully complies with the sequence rules.

Withdrawn - Objections to the Specification

6. Previous objection to the specification because the title is not descriptive is withdrawn by virtue of Applicant's amendment to the title.

7. Previous objection to the specification for lacking a titled section to describe the figures is withdrawn by virtue of Applicant's amendment to page 21.

8. Previous objection to the specification for having incomplete citations is withdrawn by virtue of Applicant's amendment deleting the incomplete citation on page 40; the specification is clear without the inclusion of a reference on page 40.

9. Previous objection to the amendment filed November 28, 2001 under 35 U.S.C. § 132 because it introduces new matter into the disclosure in Claims 22 and 26 is withdrawn. Applicant cites clear support for the subject matter in originally filed claims. Said support is persuasive to withdrawn the objection.

New - Objections to the Specification

10. The specification is objected to for lacking a clear description of the sequence portions in Table 1, as amended to refer to SEQ ID NOs:1-4. In Table 1, on pages 68-69, nucleotides 1-103,450 are noted. The relationship between SEQ ID NOs:1-4 and these nucleotides are not clear. Is the entire gene cluster represented consecutively by the 30,000 nucleotides of SEQ ID NO:1-the 30,000 nucleotides of SEQ ID NO:2-the 30,000 nucleotides of SEQ ID NO:3-the 13,600 nucleotides of SEQ ID NO:4? If this is the case, some indication of the SEQ ID NOs being consecutive is required so that the nucleotide numbers listed in the Table are clear. Clarification is required.

11. The amendment filed January 27, 2005 is objected to under 35 U.S.C. § 132(a) because it introduces new matter into the disclosure. 35 U.S.C. § 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: the incorporation by reference of PCT/GB/02072. No incorporation was made in the specification as originally filed.

Applicant is required to cancel the new matter in the reply to this Office Action.

12. The specification is objected to for numerous typographical errors in Table I. The data of Table I is also noted in Table II and Figure 4. While these sources are consistent, some inconsistencies with Table I are noted as follows:

a) "monCI" (first appearance) should be monCII
b) "ABC-" is unclear
c) "monRI" (first appearance) should be monRII
d) "monAI" (first appearance) should be monAIX
e) "loading &" is unclear
f) "monAI" (third appearance) should be monAII
g) "monAI" (fourth appearance) should be monAIII
h) "monAI" (fifth appearance) should be monAIV
i) "monA" (first appearance) should be monAV
j) "monA" (second appearance) should be monAVI
k) "monBI" (first appearance) should be monBII
l) "monA" (third appearance) should be monAVIII
m) "11 &" is unclear
n) "monA" (fourth appearance) should be monAVII
o) "monA" (fifth appearance) should be monAX.

Extensive correction is required for Table I to be consistent with the rest of the specification.

Withdrawn - Claim Objections

13. Previous objection to Claims 1-3, 6-12, 30-34, 37, 38, 46, and 47 for containing non-elected subject matter is withdrawn by virtue of Applicant's amendment.

14. Previous objection to Claim 1 for improper punctuation is withdrawn by virtue of Applicant's amendment.

New - Claim Objections

15. Claims 9 and 47 are objected to under 37 C.F.R. § 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is

required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The limitation of at least 30 or at least 60 bases does not further limit the parent claim because the smallest functional domains disclosed as the ACP domains which have 257 or 254 nucleotides; as few as 30 or 60 nucleotides (25% of the full length domain) will not maintain the enzymatic activity as required in Claim 1. Thus, these limitations are outside the scope of Claim 1.

16. Claim 31 is objected to under 37 C.F.R. § 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The limitations of monensin variants thereof in no way limits the subject matter of Claim 30 because all PKS modules/domains can be considered variants of the monensin PKS.

17. Claim 32 is objected to under 37 C.F.R. § 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The requirement that the monensin module/domain must be contiguous with a different (not naturally associated) PKS module or domain already sets forth the limitation that the "further domain" must be from a PKS other than monensin.

18. Claims 1, 3 and 11 are objected to for improper usage. The phrases "encoding for" or "encodes for" or "encoded for" are improper in the art. The phrase should be ---coding for--- or ---encodes---, etc. See Claim 30 for correct usage. Correction is required.

19. Claim 46 is objected to for redundant language. The phrase "90% identical with the amino acid sequence of the corresponding polypeptide in SE QID NO:22" is lengthy and unnecessary. It is sufficient to say ---90% identical to SEQ ID NO:22--- as is proper, accepted language. Correction is required.

20. The following are not objections about the further limiting nature of claims, but a clarification for the record of the scope of the claims.

Claim 46, dependent from Claim 1, requires a part of SEQ ID NO:22 (enough for particular enzyme activity) that is invariant (not 90% identical). Claim 46 further limit Claim 1 because the rest of the DNA claimed (note open language) can vary but must maintain an overall 90% identity to a sequence that encodes SEQ ID NO:22. If this is not Applicant's intent, an independent claim to 90% identical to SEQ ID NO:22 must be written.

Claim 48, dependent from Claim 1, requires a part of 12448-24564 of SEQ ID NO:2 (disclosed as exactly encoding SEQ ID NO:22); this part must be sufficient to encode an enzyme activity as required in Claim 1 (further limiting because of exact nucleotide sequence, not merely encoding language as in Claim 1). The remainder of the sequence is free to vary.

Withdrawn - Claim Rejections - 35 U.S.C. § 112, second paragraph

21. Previous rejection of Claims 6-7 under 35 U.S.C. § 112, second paragraph, as being indefinite for the phrase "polypeptides set out below" is withdrawn by virtue of Applicant's cancellation and/or amendment of said claims.

22. Previous rejection of Claims 6-7 under 35 U.S.C. § 112, second paragraph, as being indefinite for the activity of "polyketide synthase multienzyme" is withdrawn by virtue of Applicant's amendment removing the term.

23. Previous rejection of Claim 11 under 35 U.S.C. § 112, second paragraph, as being indefinite for a "corresponding polypeptide" is withdrawn by virtue of Applicant's amendment.

24. Previous rejection of Claims 30-34 and 37-38 under 35 U.S.C. § 112, second paragraph, as being indefinite for the abbreviation "PKS" is withdrawn by virtue of Applicant's amendment defining the abbreviation upon its first occurrence in the claims.

25. Previous rejection of Claims 30-34 and 37-38 under 35 U.S.C. § 112, second paragraph, as being indefinite for the phrase "said modules or a domain" is withdrawn by virtue of Applicant's amendment.

26. Previous rejection of Claims 30-34 and 37-38 under 35 U.S.C. § 112, second paragraph, as being indefinite for the abbreviation "AT" is withdrawn by virtue of Applicant's amendment defining the abbreviation upon its first occurrence in the claims.

New or Maintained - Claim Rejections - 35 U.S.C. § 112, second paragraph

27. Previous rejection of Claims 30-34 and 37-38 under 35 U.S.C. § 112, second paragraph, as being indefinite for the phrase "an ery loading module" is maintained. Claims 35 and 49 have been added. Applicant's arguments have been fully considered but are not deemed persuasive for the following reasons. Applicant argues that an amendment to "**the** erythromycin loading module" (emphasis added) renders the claim clear. The Examiner would agree, except the amendment, as filed, is to ---**an** erythromycin loading module--- (emphasis added), which raised the same issue previously addressed. As previously noted, the Examiner knows of only a single example of an erythromycin PKS with a single loading module. The article "an" indicates any (one of more than one) erythromycin loading module. Clarification is required.

28. Previous rejection of Claim 34 under 35 U.S.C. § 112, second paragraph, as being indefinite for the phrase "derived from" is maintained; Claim 49 has been added. Applicant's arguments have been fully considered but are not deemed persuasive for the following reasons. Applicant argues that the amendment to more clearly describe the derivation clarifies the claims; the Examiner disagrees. Must the only change between the monensin KS domain and a KSq domain be the "q" (the q in KSq stands for a point mutation of a q in the active site of a KS domain where active KS domains have a cysteine)? Derived does not limit to this, but the claim language implies it. Clarification is required.

29. Claims 1, 7-12, and 46-48 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase "at least part of MonAIV is a **polypeptide** having

at least one **enzyme** activity ...selected from the group consisting of [KS, AT, DH, KR, ACP, and ER activities]" (emphasis added) is unclear as to its open language, the polypeptide nature, and the enzymatic activity. Firstly, the below language more clearly sets forth the open language intended by the claim. Secondly, this open language is necessary because the polypeptide fragments themselves do not necessarily have the noted activities, which are functional in the multifunctional PKS enzyme as a whole. Thirdly, not all the activities noted are enzyme activities since the ACP does not catalyze a reaction. The Examiner suggests the following language to clarify the above points and clearly link to support found in the specification as originally filed; these are useful in clearly claiming subject matter as in Claims 7 and 8.

---Claim 1. An isolated DNA sequence comprising a nucleotide sequence encoding at least part of the MonAIV polypeptide wherein said at least part is a fragment of MonAIV having at least one of the following activities:

a) ·ketosynthase (KS) activity,
b) acyl transferase (AT) activity,
c) dehydratase (DH) activity,
d) ketoreductase (KR) activity,
e) acyl-carrier protein (ACP) activity, and/or
f) enoyl reductase (ER) activity.---

30. Claim 2 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase "the complete monensin gene cluster" is unclear if the term encompasses every gene listed in Table I and, if so, exactly SEQ ID NOs:1-4 in their entirety. If not every gene in Table I, which ones - just the PKS genes? Must the DNA only encode the proteins as disclosed? Clarification on all these points is required.

31. Claims 4-5 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The requirement of "at least a part of one or more of the following genes" is unclear. Must the part have the activity noted in Table I, which "part" would be analogous to the part required in Claim 1 (a parent claim of Claim 4)? If not, how small a "part" is allowed to read on the instant claim? Moreover, the indication of alleles, mutants, and variants is unclear if a significant portion of the genes in Table I are requires since Claim 5 must further limit the scope of Claim 4, not broaden it by allowing for alterations in the sequence intended. Clarification is required.

32. Claim 8 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The nature of "DNA sequence encoding any one or more of the domains as set out in Table 1" is confusing. Table 1 sets out nucleotide sequences of full-length proteins, some of which contain domains. Are only the proteins with domains included? Must the sequence only encode or must the exact DNA sequence be used as described in Table I? Must the domain be in addition to the domain that meets the limitations for Claim 1 (the parent claim). Clarification on all these points is required.

33. Claims 9 and 47 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is confusing on how such short sequences can retain the

activities as required in Claim 1. No domains of such minimal length are described in Table 1 or the art for other PKS systems. Clarification is required.

34. Claims 30-34, 37, 38, and 49 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The overall claim structure of Claim 30 is very confusing. Specifically, the paragraph nature is difficult to read wherein paragraphs and/or tabs within would assist the skilled artisan in understanding the scope. Additionally, the phrase "to which said monensin module or domain from MonAIV is not naturally contiguous" is unclear as to whether the phrase modifies only the further extension module or if the phrase extends to the loading module as well. The Examiner suggests the following alternative claim language:

---30. A DNA sequence comprising a nucleotide sequence encoding at least one polyketide synthase (PKS) comprising a loading module and a plurality of extension modules,
wherein at least one of said modules, or at least a domain thereof, is a module or domain from MonAIV,
and wherein said MonAIV module or domain is contiguous with a module or domain not naturally associated thereto;
provided that the nucleotide sequence is not comprised of
the erythromycin loading module followed by
the first and second extension modules or the erythromycin PKS followed by
the erythromycin chain-terminating thioesterase
except that the AT domain of the first extension module is substituted with the ethylmalonyl-specific AT5 of MonAIV.---

35. Claims 33-34 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase "adapted to load" is confusing. Must the loading module be mutated? Or can the loading module simply be associated with an extension module not

usually associated with a loading module that loads the particular starting unit not used by the extension module? Clarification is required.

36. Claim 49 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The antecedent basis of "said monensin extension module" is unclear since the monensin modules/domains of Claim 30 need not be only extension modules. Clarification is required.

Withdrawn - Claim Rejections - 35 U.S.C. § 112, first paragraph

37. Previous rejection of Claims 1-2, 8-12, and 47 under 35 U.S.C. § 112, first paragraph, written description, is withdrawn by virtue of Applicant's limiting the claimed invention to having at least fragments of the MonAIV disclosed (SEQ ID NO:22) and having activity.

38. Previous rejection of Claims 3, 6, and 7 under 35 U.S.C. § 112, first paragraph, written description, is withdrawn by virtue of Applicant's amendment and/or cancellation of said claims.

39. Previous rejection of Claims 30-34 and 37-38 under 35 U.S.C. § 112, first paragraph, written description, is withdrawn by virtue of Applicant's amendment of said claims.

40. Previous rejection of Claims 1-3, 6-12, 30-34, 37, 38, and 46-47 under 35 U.S.C. § 112, first paragraph, scope of enablement, is withdrawn by virtue of Applicant's amendment and/or reconsideration by the Examiner.

New - Claim Rejections - 35 U.S.C. § 112, first paragraph

41. Claim 5 and 31 are rejected under 35 U.S.C. § 112, first paragraph, written description, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The instant claims are drawn to DNA sequence that is claimed without any structural limitations; the terms "allele, mutation, or other variant" have no specifically defined breadth and, thus, cannot be considered to structurally limit the claimed subject matter.

The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as be structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." University of California v. Eli Lilly and Co., 1997 U.S. App. LEXIS 18221, at *23, quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original). To fully describe a genus of genetic material, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these.

In the instant specification, the MonAIV gene is described as nucleotides 42448-54564 (SEQ ID NO:2 from 12448-24564) that encodes a 4039 amino acid protein that is a polyketide

synthase multienzyme having domains as described in Figure 3 (see also Tables I and II). Due to the lack of structural limitation in the claims, the DNA is only limited according to the functional characteristics of the enzyme it encodes, as implied by "encoding ... a polypeptide ... for the biosynthesis of monensin". Therefore, the claimed DNA can have any structure while retaining the implied function. Thus, one of skill in the art would be unable to predict the structure of other members of this genus by virtue of the instant disclosure.

42. Claim 46 is rejected under 35 U.S.C. § 112, first paragraph, written description, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The instant claims are drawn to a DNA product encoding a variant having a 90% sequence identity to MonAIV (also having exactly at least one domain - or active fragment thereof - of SEQ ID N:22) wherein the portions not exactly part of SEQ ID NO:22 lack a requisite function.

The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as be structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." University of California v. Eli Lilly and Co., 1997 U.S. App. LEXIS 18221, at *23, quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original). To fully describe a genus of genetic material, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the

common characteristics of the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these.

The instant specification teaches SEQ ID NOs:1-4 that together make up the entirety of the monensin gene cluster of 103,600 nucleotides. Large portions of SEQ ID NOs:1-4 encode proteins involved in the biosynthesis of monensin as disclosed in Table I. Each of the proteins involved has a distinct function, whether that be a methyl transferase and a monensin resistance gene, both considered "accessory proteins", or MonAI and MonAII, which catalyze analogous, but distinct reactions (note different "substrate" as pictured in Figure 3 of the instant application). The instant specification describes the genus relating to said SEQ ID NOs with both sequence identity (or fragment) limitations and functional limitations. However, the genus of the instant claims also contains polynucleotides within the sequence identity (or fragment) limitations, but having different function. Applicants have not fully described a genus that has sequence identity limitations in the absence of functional limitations.

Withdrawn - Claim Rejections - 35 U.S.C. § 101

43. Previous rejection of Claims 1-3, 6-9, 46, and 47 under 35 U.S.C. § 101, utility, is withdrawn by virtue of Applicant's amendment inserting "isolated" in Claim 1. Moreover, the Examiner notes that Claim 30 need not be limited to isolated by virtue of the manipulation required in the language of the claim.

Withdrawn - Claim Rejections - 35 U.S.C. § 102

44. Previous rejection of Claims 1, 3, 6-10, 12 and 47 under 35 U.S.C. § 102(b) as being anticipated by GenBank Accession Number AF144047 is withdrawn by virtue of Applicant's amendment. The requirement of functionality of the encoded protein is not disclosed in AF144047; while the reference teaches a 247 amino acid polyketide synthase protein, no specific description of these specific activities (known PKS activities) is found in this prior art.

45. Previous rejection of Claims 1-3, 6-10, 12 and 47 under 35 U.S.C. § 102(b) as being anticipated by GenBank Accession Number U78289 is withdrawn by virtue of Applicant's amendment requiring a significant (encoding an activity) contiguous portion of MonAIV (SEQ ID NO:22) to read on the claims.

The Examiner herein notes clearly and for the record that in the pending claims, the term MonAIV, which means the polypeptide, is read as SEQ ID NO:22 (a polypeptide of 4039 amino acids in the sequence listing as filed) since this is the only disclosure about the polypeptide MonAIV. Nowhere in the specification is MonAIV described as any other monensin PKS having a different sequence.

46. Previous rejection of Claims 11, 30-34 and 37-38 under 35 U.S.C. § 102(b) as being anticipated by Kuhstoss *et al.* is withdrawn by virtue of Applicant's amendment requiring a significant (encoding an activity) contiguous portion of MonAIV (SEQ ID NO:22) to read on the claims.

Claim Rejections - 35 U.S.C. § 102/103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

47. Claims 1, 7, 9-11, 30-33, 35, 37, 38, are 47-49 are rejected under 35 U.S.C. § 102(b) as anticipated by or, in the alternative, under 35 U.S.C. § 103(a) as obvious over Leadlay *et al.* (WO 98/01546); this is an *In Re* Best-type rejection (see M.P.E.P. § 2112). The instant claims are drawn to DNA comprising a sequence encoding acyltransferase (AT) domain 5 of MonAIV of the monensin polyketide synthase. Moreover, the claims are drawn to DNA encoding a hybrid PKS including AT5 of MonAIV. The claims are also drawn to vectors and host cells comprising said DNA.

Leadlay *et al.* teach that at least part of the monensin gene and modular organization is known through gene sequence analysis (see page 15, lines 30-36). More specifically, Leadlay *et al.* teach plasmid pC-ATX and its expression in *S. erythraea* JC2 to produce ketide derivatives (see Examples 53-55, pages 99-103). Said plasmid contains "the malonyl-CoA:ACP acyltransferase from a putative type I PKS gene cluster cloned from *Streptomyces cinnamonensis* ATCC 14513 (producer of the polyether polyketide monensin)." This portion from the monensin

cluster is substituted for the AT of the first extension module of ery_{LOAD}-ery_{ext1}-ery_{ext2}-ery_{TE} to produce pC-ATX. The Examiner will set forth reasoning to conclude that the portion of the monensin cluster used by Leadlay *et al.* is AT5 of MonAIV reading on the instant claims. The reasoning is as follows:

a) The DNA cloned by Leadlay *et al.* seems to be taken from the same source for the following reasons. Leadlay *et al.* describe using ATCC 14513 as the source of the monensin PKS DNA; however, ATCC 14513 is a *Gilocladium sp.* (see attachment). Thus, the ATCC number quoted from Leadlay *et al.* seems to be a typographical error, and it is reasonable to assume that Leadlay *et al.* used ATCC 15413 as the source for the DNA, which is the same source *S. cinnamonensis* strain used in the instant application.
b) The DNA cloned by Leadlay *et al.* is an AT domain with ethylmalonyl specificity for the following reasons. Leadlay *et al.* describe the AT domain cloned from *S. cinnamonensis* as malonyl-specific on page 99. However, on page 100, Leadlay *et al.* further describe that after DNA sequencing, the monensin AT domain used has "an unusual sequence motif in the putative substrate recognition part of the domain wich [sic] was substantially different from previously described malonate- or methylmalonate-specific CoA:ACP acyltransferases". But most convincing is that upon expression in JC2, products from the hybrid PKS were isolated and characterized whose chemical structures are found on the top of page 103 (see attached). These products of the hybrid PKS reveal the ethyl-malonyl specificity of the AT domain used by virtue of the ethyl moiety attached to C3 (see numbering in attachment) since the AT1 domain is responsible for the side chain on this carbon. Thus, despite Leadlay *et al.* originally characterizing the AT domain used from the monensin PKS as malonyl-specific, the evidence (both the lack of sequence similarity with other malonyl and methylmalonyl ATs and the products produced by the hybrid PKS) clearly indicates that the monensin AT used was ethyl-specific.
c) As disclosed in the instant specification, the only ethyl-specific AT domain in monensin is that of AT5 (see Table I).

Thus, taking the logic presented above all together, it **must** flow from the prior art that the AT domain used in the hybrid pC-ATX of Leadlay *et al.* is the ethylmalonyl-specific AT5 domain of monensin PKS from *S. cinnamonensis*. If the Examiner's reasoning concerning the typographical error in the ATCC number disclosed in Leadlay *et al.* is correct, then Leadlay *et al.* use the ethylmalonyl-specific AT5 domain of monensin PKS from *S. cinnamonensis* ATCC 15413 just as encompassed by the instant claims.

Claim Rejections - 35 U.S.C. § 103

48. Claim 12 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Leadlay *et al.* (WO 98/01546). The instant claims are drawn to hybridization probes based on AT5 of the monensin MonAIV.

Leadlay *et al.* teach AT5 of monensin MonAIV as described above. Leadlay *et al.*, while teaching the use of PKS probes to identify novel PKS gene clusters, do not expressly teach using the monensin sequence as a probe.

At the time of the invention, it would have been obvious to one of ordinary skill in the art to use the monensin AT5 sequence as a probe because all PKS genes are useful as probes, as noted by Leadlay *et al.* Moreover, one would have been motivated to use the monensin AT5 sequence as a probe to find portions of the monensin gene cluster, as yet unknown yet useful, also as noted by Leadlay *et al.*

Examiner's Comments on the Prior Art

49. The following are to clarify the record concerning the pertinent prior art cited in the IDS:

a) Arrowsmith *et al.* teach hybridizing actI and actIII probes to an *S. cinnamonensis* library for the purpose of isolating a PKS gene cluster; however, the sequence isolated is not a PKS gene cluster (see Abstract) nor does it align with MonAIV.
b) Donovan *et al.* teach isolating about 50kB of *S. cinnamonensis* using an actI probe. The sequence is disclosed as not being the complete gene cluster since it can complement only 11 of 18 monensin-minus mutants of *S. cinnamonensis* and it, alone, cannot support monensin production in *S. lividans*. Despite the likelihood that a DNA sequence of this size, linked to monenin production, contains at least a domain of MonAIV, no specific evidence can be provided to render Donovan *et al.* prior art on Claim 1. This is particularly poignant recognizing the actI probes do not always pull out PKS gene clusters (see Arrowsmith *et al.* above).
c) Malpartida *et al.* hybridize actI and III probes to a library of *S. cinnamonensis* to indicate that a PKS gene cluster can be found within the genome; however, no further isolation and/or characterization of the *S. cinnamonensis* sequence was done to evidence its MonAIV nature.
d) Ashworth *et al.* does not teach the isolation of any monensin PKS DNA.

Conclusion

50. Claims 1-5, 7-12, 30-34, 37, 38, and 46-49 are not allowed for the reasons identified in the numbered sections of this Office action. Applicants must respond to the objections/rejections in each of the numbered sections in this Office action to be fully responsive in prosecution. The instant Office action is non-final by virtue of the new art rejection set forth.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kathleen M. Kerr whose telephone number is (571) 272-0931. The examiner can normally be reached on Monday through Friday, from 9:00am to 6pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathupura Achutamurthy can be reached on (571) 272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Kathleen M Kerr
Primary Examiner
Art Unit 1652

April 15, 2005